

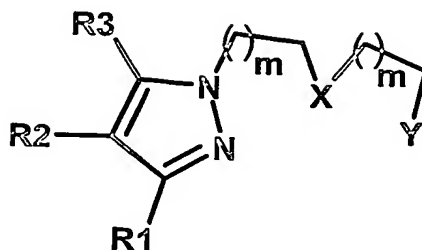
BIFUNCTIONAL TRIDENTATE PYRAZOLYL CONTAINING LIGANDS
FOR RE, TC AND MN TRICARBONYL COMPLEXES

This invention lies in the field of
5 radiopharmaceuticals and provides new chelating agents to
link biomolecules and carbonyl moieties for labeling with
technetium and rhenium. In particular the invention relates
to bifunctional tridentate pyrazolyl-polyamines, pyrazolyl-
aminothioethers, pyrazolyl-polythioethers, pyrazolyl-
10 aminophosphines and pyrazolyl-thioetherphosphines which
stabilize the moieties $[M(CO)_3]^+$ ($M = Re, Tc, Mn$) and bind to
biomolecules which accumulate in diseased tissues. The
invention relates to the chelators as such, to chelators
coupled to a biomolecule and to either of these complexed
15 with carbonyl. In addition the invention relates to a kit for
providing radiolabeled biomolecules and to the use of such
radiolabeled molecules in diagnosis and therapy.

The diagnosis and therapy of cancer still needs a
significant input from the chemical, radiochemical and
20 pharmaceutical point of view. Tumour seeking compounds stable
in vitro and *in vivo*, with high specific activity and
specificity are still an important issue in the
radiopharmaceutical field. Since the publication of
international patents on $[Re(CO)_3]^+$ and $[Tc(CO)_3]^+$ [1] a
25 significant interest has appeared in this oxidation state,
which opens new perspectives on pharmaceutical and Nuclear
Medicine fields. The search for new chelating agents is
essential as they are determinant for the uptake of
biological vectors. Several chelating agents have been
30 described in patents [1, 2] and publications [3, 4, 5].

It is the object of the present invention to enlarge
the family of bifunctional chelating agents.

This is achieved by the invention by chelating agents of the general formula:



10 wherein m is 0 or 1;

X is NR_4 or S ;

Y is SR_5 , NHR_5 or $P(R_5)_2$;

R_1 and R_3 are the same or different and are selected from H , alkyl or aryl;

15 R_2 is H , $COOH$, NHR_6 or $(CH_2)_nCOOR_6$;

R_4 is H , alkyl, aryl, $(CH_2)_nCOOR_6$ or $(CH_2)_nOR_6$;

R_5 is H , alkyl, aryl, $(CH_2)_nCOOR_6$ or $(CH_2)_nOR_6$;

R_6 is H , alkyl or aryl;

n is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10; and

20 when $R_1 = R_3 = CH_3$, R_2 , R_4 and R_5 are not all three H .

These molecules combine two functions. One is for the stabilization of metal centers, including radioactive metals, and comprises different donor atom sets, and the other is a functional group for binding to the molecule of interest.

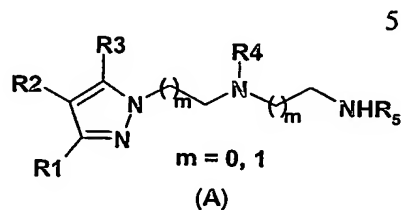
25 The alkyl is a C_1 alkyl, C_2 alkyl, C_3 alkyl, C_4 alkyl, C_5 alkyl or C_6 alkyl, in particular selected from methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, isohexyl (2-methylpentyl), neohexyl (2,2-dimethylbutyl), 3-methylpentyl, 30 2,3- dimethylbutyl.

The aryls are monocyclic, C_5 - C_8 , or polycyclic C_{10} - C_{18} , and are optionally substituted with alkyl, carboxy, oxo,

amino, alkoxy or aldehyde groups.

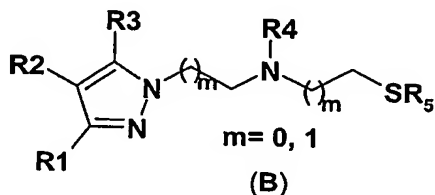
n is 2, 3, 4, 5 or 6 and preferably 2, 3 or 4.

The chelating agent is for example a pyrazolyl-polyamine of the general formula:



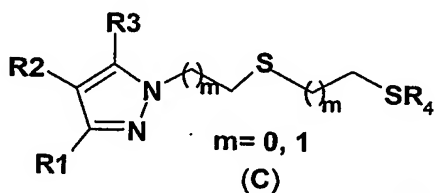
10 wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined above.

Alternatively, the chelating agent is a pyrazolyl-aminothioether of the general formula:



wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined above.

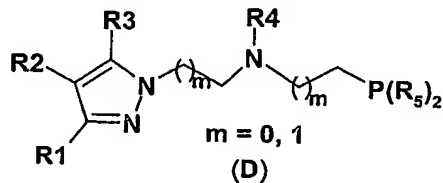
In yet another embodiment the chelating agent is a
20 pyrazolyl-polythioether of the general formula:



25

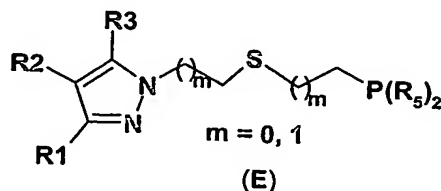
wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined above.

In yet another embodiment the chelating agent is a
pyrazolyl-aminophosphine of the general formula :



wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined above.

In a further embodiment the chelating agent is a pyrazolyl-thioetherphosphine of the general formula :



wherein R_1 , R_2 , R_3 , R_4 and R_5 are as defined above.

10 The invention provides more particularly chelating agents of formula I, wherein X and Y are N, R_6 is H, C_1 alkyl, C_2 alkyl, C_3 alkyl, C_4 alkyl, C_5 alkyl or C_6 alkyl, monocyclic aryls, preferably phenyl or benzyl, or polycyclic C_{10} - C_{18} aryls, optionally substituted with alkyl, carboxy, oxo
15 amino, alkoxy or aldehyde groups, or a biomolecule and R_1 , R_3 , R_3 , R_4 and R_5 are as listed in Table 1.

In another embodiment the invention relates to chelating agents of formula I, wherein X and Y are S, R_6 is H, C_1 alkyl, C_2 alkyl, C_3 alkyl, C_4 alkyl, C_5 alkyl or C_6
20 alkyl, monocyclic aryls, preferably phenyl or benzyl, or polycyclic C_{10} - C_{18} aryls, optionally substituted with alkyl, carboxy, oxo amino, alkoxy or aldehyde groups, or a biomolecule and R_1 , R_2 , R_3 , R_4 and R_5 are as listed in Table 1.

25 In yet another embodiment chelating agents of formula I are provided, wherein X is N and Y is S, R_6 is H, C_1 alkyl, C_2 alkyl, C_3 alkyl, C_4 alkyl, C_5 alkyl or C_6 alkyl, monocyclic aryls, preferably phenyl or benzyl, or polycyclic C_{10} - C_{18} aryls, optionally substituted with alkyl, carboxy, oxo amino,
30 alkoxy or aldehyde groups, or a biomolecule and R_1 , R_2 , R_3 , R_4 and R_5 are as listed in Table 1.

According to a further aspect thereof the invention

relates to chelating agents of formula I, wherein X is S and Y are N, R₆ is H, C₁ alkyl, C₂ alkyl, C₃ alkyl, C₄ alkyl, C₅ alkyl or C₆ alkyl, monocyclic aryls, preferably phenyl or benzyl, or polycyclic C₁₀-C₁₈ aryls, optionally substituted
5 with alkyl, carboxy, oxo amino, alkoxy or aldehyde groups, or a biomolecule and R₁, R₂, R₃, R₄ and R₅ are as listed in Table 1.

According to another aspect of the invention, chelating agents of formula I are provided, wherein X is N
10 and Y is P, R₆ is H, C₁ alkyl, C₂ alkyl, C₃ alkyl, C₄ alkyl, C₅ alkyl or C₆ alkyl, monocyclic aryls, preferably phenyl or benzyl, or polycyclic C₁₀-C₁₈ aryls, optionally substituted with alkyl, carboxy, oxo amino, alkoxy or aldehyde groups, or a biomolecule and R₁, R₂, R₃, R₄ and R₅ are as listed in Table
15 1.

In another embodiment the invention relates to chelating agents of formula I, wherein X is S and Y is P, R₆ is H, C₁ alkyl, C₂ alkyl, C₃ alkyl, C₄ alkyl, C₅ alkyl or C₆ alkyl, monocyclic aryls, preferably phenyl or benzyl, or
20 polycyclic C₁₀-C₁₈ aryls, optionally substituted with alkyl, carboxy, oxo amino, alkoxy or aldehyde groups, or a biomolecule and R₁, R₂, R₃, R₄ and R₅ are as listed in Table 1.

The chelating agents of the invention are
25 particularly suited to link biomolecules with carbonyl moieties in order to arrive at labeled biomolecules having a high specificity for the target. In formula I R₆ can thus be a biomolecule.

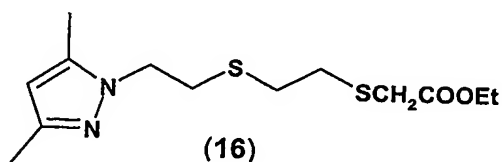
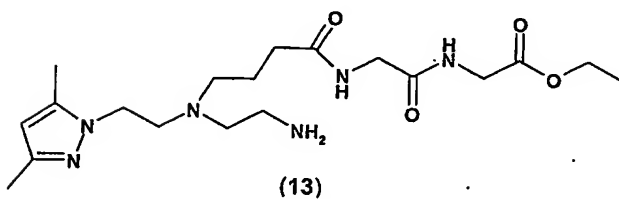
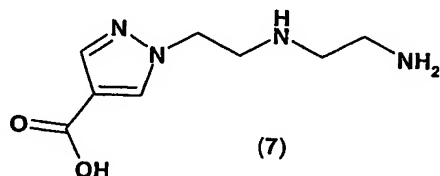
The possible positions of the biomolecules (BM) are
30 shown in Fig. 1.

The biomolecule can be anything that is useful in the treatment and diagnosis of tumors and can be coupled to the

chelators of the invention. The skilled person will be able to establish for which biomolecules the chelators of the invention can be used. In particular the biomolecule is selected from amino acids, peptides, proteins,
5 oligonucleotides, polynucleotides, sugars.

More specifically, the biomolecule is selected from the group consisting of antibodies, ligands of tumor receptors, such as CCK, thioglucose, glucosamine, somatostatin, neurotensin, bombesin, CCK, annexin,
10 interleukins, growth factors, steroid hormones and molecules binding to GPIIb/IIIa receptors. Other biomolecules can be glucose, thioglucose, neurotransmitters, inhibitors of the tyrosine kinase activity such as benzothiopyranones, anilinophthalimides, quinazolines, pyridopyrimidines and
15 pyrrolopyrimidines.

Particular agents of the invention are the following:



All of the chelating agents, either with or without a biomolecule coupled thereto can be complexed with a carbonyl

moiety of the formula $[M(CO)_3]^+$, wherein M is rhenium (Re), technetium (Tc) or Manganese (Mn).

The chelating agents of the invention are molecules according to formula I wherein X and Y can be either N and N, N and S, S and N, S and S, N and P, or S and P. Each of these combinations can be combined with various combinations of R₁, R₂, R₃, R₄ and R₅. All possible combinations of R₁, R₂, R₃, R₄ and R₅ are listed in Table 1. In Table 1 alkyl is a C₁ alkyl, C₂ alkyl, C₃ alkyl, C₄ alkyl, C₅ alkyl or C₆ alkyl, in particular selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl (2-methylpentyl), neohexyl (2,2-dimethylbutyl), 3-methylpentyl, 2,3-dimethylbutyl; the aryl is monocyclic, C₅-C₈, or polycyclic, C₁₀-C₁₈, and optionally substituted with alkyl, carboxy, oxo, amino, alkoxy or aldehyde groups and is in particular phenyl or benzyl, and n is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. R₆ is H, alkyl, aryl or a biomolecule as defined above. Substituting each of the above variables into the table will give all compounds of claim 1 that are herewith disclosed.

Table 1

R1	R2	R3	R4	R5
H	H	H	H	H
H	H	H	H	alkyl
H	H	H	H	aryl
H	H	H	H	(CH ₂) _n COOR ₆
H	H	H	H	(CH ₂) _n OR ₆
H	H	H	alkyl	H
H	H	H	alkyl	alkyl
H	H	H	alkyl	aryl
H	H	H	alkyl	(CH ₂) _n COOR ₆
H	H	H	alkyl	(CH ₂) _n OR ₆
H	H	H	aryl	H

H	H	H	aryl	alkyl
H	H	H	aryl	aryl
H	H	H	aryl	(CH ₂) _n COOR ₆
H	H	H	aryl	(CH ₂) _n OR ₆
H	H	H	(CH ₂) _n COOR ₆	H
H	H	H	(CH ₂) _n COOR ₆	alkyl
H	H	H	(CH ₂) _n COOR ₆	aryl
H	H	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	H	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	H	H	(CH ₂) _n OR ₆	H
H	H	H	(CH ₂) _n OR ₆	alkyl
H	H	H	(CH ₂) _n OR ₆	aryl
H	H	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	H	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	H	alkyl	H	H
H	H	alkyl	H	alkyl
H	H	alkyl	H	aryl
H	H	alkyl	H	(CH ₂) _n COOR ₆
H	H	alkyl	H	(CH ₂) _n OR ₆
H	H	alkyl	alkyl	H
H	H	alkyl	alkyl	alkyl
H	H	alkyl	alkyl	aryl
H	H	alkyl	alkyl	(CH ₂) _n COOR ₆
H	H	alkyl	alkyl	(CH ₂) _n OR ₆
H	H	alkyl	aryl	H
H	H	alkyl	aryl	alkyl
H	H	alkyl	aryl	aryl
H	H	alkyl	aryl	(CH ₂) _n COOR ₆
H	H	alkyl	aryl	(CH ₂) _n OR ₆
H	H	alkyl	(CH ₂) _n COOR ₆	H
H	H	alkyl	(CH ₂) _n COOR ₆	alkyl
H	H	alkyl	(CH ₂) _n COOR ₆	aryl
H	H	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	H	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	H	alkyl	(CH ₂) _n OR ₆	H
H	H	alkyl	(CH ₂) _n OR ₆	alkyl
H	H	alkyl	(CH ₂) _n OR ₆	aryl
H	H	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	H	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	H	aryl	H	H
H	H	aryl	H	alkyl
H	H	aryl	H	aryl
H	H	aryl	H	(CH ₂) _n COOR ₆

H	H	aryl	H	(CH ₂) _n OR ₆
H	H	aryl	alkyl	H
H	H	aryl	alkyl	alkyl
H	H	aryl	alkyl	aryl
H	H	aryl	alkyl	(CH ₂) _n COOR ₆
H	H	aryl	alkyl	(CH ₂) _n OR ₆
H	H	aryl	aryl	H
H	H	aryl	aryl	alkyl
H	H	aryl	aryl	aryl
H	H	aryl	aryl	(CH ₂) _n COOR ₆
H	H	aryl	aryl	(CH ₂) _n OR ₆
H	H	aryl	(CH ₂) _n COOR ₆	H
H	H	aryl	(CH ₂) _n COOR ₆	alkyl
H	H	aryl	(CH ₂) _n COOR ₆	aryl
H	H	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	H	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	H	aryl	(CH ₂) _n OR ₆	H
H	H	aryl	(CH ₂) _n OR ₆	alkyl
H	H	aryl	(CH ₂) _n OR ₆	aryl
H	H	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	H	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	COOH	H	H	H
H	COOH	H	H	alkyl
H	COOH	H	H	aryl
H	COOH	H	H	(CH ₂) _n COOR ₆
H	COOH	H	H	(CH ₂) _n OR ₆
H	COOH	H	alkyl	H
H	COOH	H	alkyl	alkyl
H	COOH	H	alkyl	aryl
H	COOH	H	alkyl	(CH ₂) _n COOR ₆
H	COOH	H	alkyl	(CH ₂) _n OR ₆
H	COOH	H	aryl	H
H	COOH	H	aryl	alkyl
H	COOH	H	aryl	aryl
H	COOH	H	aryl	(CH ₂) _n COOR ₆
H	COOH	H	aryl	(CH ₂) _n OR ₆
H	COOH	H	(CH ₂) _n COOR ₆	H
H	COOH	H	(CH ₂) _n COOR ₆	alkyl
H	COOH	H	(CH ₂) _n COOR ₆	aryl
H	COOH	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	COOH	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	COOH	H	(CH ₂) _n OR ₆	H
H	COOH	H	(CH ₂) _n OR ₆	alkyl

H	COOH	H	(CH ₂) _n OR ₆	aryl
H	COOH	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	COOH	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	COOH	alkyl	H	H
H	COOH	alkyl	H	alkyl
H	COOH	alkyl	H	aryl
H	COOH	alkyl	H	(CH ₂) _n COOR ₆
H	COOH	alkyl	H	(CH ₂) _n OR ₆
H	COOH	alkyl	alkyl	H
H	COOH	alkyl	alkyl	alkyl
H	COOH	alkyl	alkyl	aryl
H	COOH	alkyl	alkyl	(CH ₂) _n COOR ₆
H	COOH	alkyl	alkyl	(CH ₂) _n OR ₆
H	COOH	alkyl	aryl	H
H	COOH	alkyl	aryl	alkyl
H	COOH	alkyl	aryl	aryl
H	COOH	alkyl	aryl	(CH ₂) _n COOR ₆
H	COOH	alkyl	aryl	(CH ₂) _n OR ₆
H	COOH	alkyl	(CH ₂) _n COOR ₆	H
H	COOH	alkyl	(CH ₂) _n COOR ₆	alkyl
H	COOH	alkyl	(CH ₂) _n COOR ₆	aryl
H	COOH	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	COOH	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	COOH	alkyl	(CH ₂) _n OR ₆	H
H	COOH	alkyl	(CH ₂) _n OR ₆	alkyl
H	COOH	alkyl	(CH ₂) _n OR ₆	aryl
H	COOH	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	COOH	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	COOH	aryl	H	H
H	COOH	aryl	H	alkyl
H	COOH	aryl	H	aryl
H	COOH	aryl	H	(CH ₂) _n COOR ₆
H	COOH	aryl	H	(CH ₂) _n OR ₆
H	COOH	aryl	alkyl	H
H	COOH	aryl	alkyl	alkyl
H	COOH	aryl	alkyl	aryl
H	COOH	aryl	alkyl	(CH ₂) _n COOR ₆
H	COOH	aryl	alkyl	(CH ₂) _n OR ₆
H	COOH	aryl	aryl	H
H	COOH	aryl	aryl	alkyl
H	COOH	aryl	aryl	aryl
H	COOH	aryl	aryl	(CH ₂) _n COOR ₆
H	COOH	aryl	aryl	(CH ₂) _n OR ₆

H	COOH	aryl	(CH ₂) _n COOR ₆	H
H	COOH	aryl	(CH ₂) _n COOR ₆	alkyl
H	COOH	aryl	(CH ₂) _n COOR ₆	aryl
H	COOH	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	COOH	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	COOH	aryl	(CH ₂) _n OR ₆	H
H	COOH	aryl	(CH ₂) _n OR ₆	alkyl
H	COOH	aryl	(CH ₂) _n OR ₆	aryl
H	COOH	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	COOH	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	NHR ₆	H	H	H
H	NHR ₆	H	H	alkyl
H	NHR ₆	H	H	aryl
H	NHR ₆	H	H	(CH ₂) _n COOR ₆
H	NHR ₆	H	H	(CH ₂) _n OR ₆
H	NHR ₆	H	alkyl	H
H	NHR ₆	H	alkyl	alkyl
H	NHR ₆	H	alkyl	aryl
H	NHR ₆	H	alkyl	(CH ₂) _n COOR ₆
H	NHR ₆	H	alkyl	(CH ₂) _n OR ₆
H	NHR ₆	H	aryl	H
H	NHR ₆	H	aryl	alkyl
H	NHR ₆	H	aryl	aryl
H	NHR ₆	H	aryl	(CH ₂) _n COOR ₆
H	NHR ₆	H	aryl	(CH ₂) _n OR ₆
H	NHR ₆	H	(CH ₂) _n COOR ₆	H
H	NHR ₆	H	(CH ₂) _n COOR ₆	alkyl
H	NHR ₆	H	(CH ₂) _n COOR ₆	aryl
H	NHR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	NHR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	NHR ₆	H	(CH ₂) _n OR ₆	H
H	NHR ₆	H	(CH ₂) _n OR ₆	alkyl
H	NHR ₆	H	(CH ₂) _n OR ₆	aryl
H	NHR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	NHR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	NHR ₆	alkyl	H	H
H	NHR ₆	alkyl	H	alkyl
H	NHR ₆	alkyl	H	aryl
H	NHR ₆	alkyl	H	(CH ₂) _n COOR ₆
H	NHR ₆	alkyl	H	(CH ₂) _n OR ₆
H	NHR ₆	alkyl	alkyl	H
H	NHR ₆	alkyl	alkyl	alkyl
H	NHR ₆	alkyl	alkyl	aryl

H	NHR ₆	alkyl	alkyl	(CH ₂) _n COOR ₆
H	NHR ₆	alkyl	alkyl	(CH ₂) _n OR ₆
H	NHR ₆	alkyl	aryl	H
H	NHR ₆	alkyl	aryl	alkyl
H	NHR ₆	alkyl	aryl	aryl
H	NHR ₆	alkyl	aryl	(CH ₂) _n COOR ₆
H	NHR ₆	alkyl	aryl	(CH ₂) _n OR ₆
H	NHR ₆	alkyl	(CH ₂) _n COOR ₆	H
H	NHR ₆	alkyl	(CH ₂) _n COOR ₆	alkyl
H	NHR ₆	alkyl	(CH ₂) _n COOR ₆	aryl
H	NHR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	NHR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	NHR ₆	alkyl	(CH ₂) _n OR ₆	H
H	NHR ₆	alkyl	(CH ₂) _n OR ₆	alkyl
H	NHR ₆	alkyl	(CH ₂) _n OR ₆	aryl
H	NHR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	NHR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	NHR ₆	aryl	H	H
H	NHR ₆	aryl	H	alkyl
H	NHR ₆	aryl	H	aryl
H	NHR ₆	aryl	H	(CH ₂) _n COOR ₆
H	NHR ₆	aryl	H	(CH ₂) _n OR ₆
H	NHR ₆	aryl	alkyl	H
H	NHR ₆	aryl	alkyl	alkyl
H	NHR ₆	aryl	alkyl	aryl
H	NHR ₆	aryl	alkyl	(CH ₂) _n COOR ₆
H	NHR ₆	aryl	alkyl	(CH ₂) _n OR ₆
H	NHR ₆	aryl	aryl	H
H	NHR ₆	aryl	aryl	alkyl
H	NHR ₆	aryl	aryl	aryl
H	NHR ₆	aryl	aryl	(CH ₂) _n COOR ₆
H	NHR ₆	aryl	aryl	(CH ₂) _n OR ₆
H	NHR ₆	aryl	(CH ₂) _n COOR ₆	H
H	NHR ₆	aryl	(CH ₂) _n COOR ₆	alkyl
H	NHR ₆	aryl	(CH ₂) _n COOR ₆	aryl
H	NHR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	NHR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	NHR ₆	aryl	(CH ₂) _n OR ₆	H
H	NHR ₆	aryl	(CH ₂) _n OR ₆	alkyl
H	NHR ₆	aryl	(CH ₂) _n OR ₆	aryl
H	NHR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	NHR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	H	H	H

H	(CH ₂) _n COOR ₆	H	H	alkyl
H	(CH ₂) _n COOR ₆	H	H	aryl
H	(CH ₂) _n COOR ₆	H	H	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	H	H	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	H	alkyl	H
H	(CH ₂) _n COOR ₆	H	alkyl	alkyl
H	(CH ₂) _n COOR ₆	H	alkyl	aryl
H	(CH ₂) _n COOR ₆	H	alkyl	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	H	alkyl	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	H	aryl	H
H	(CH ₂) _n COOR ₆	H	aryl	alkyl
H	(CH ₂) _n COOR ₆	H	aryl	aryl
H	(CH ₂) _n COOR ₆	H	aryl	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	H	aryl	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	H
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	alkyl
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	aryl
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	H
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	alkyl
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	aryl
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	alkyl	H	H
H	(CH ₂) _n COOR ₆	alkyl	H	alkyl
H	(CH ₂) _n COOR ₆	alkyl	H	aryl
H	(CH ₂) _n COOR ₆	alkyl	H	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	alkyl	H	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	alkyl	alkyl	H
H	(CH ₂) _n COOR ₆	alkyl	alkyl	alkyl
H	(CH ₂) _n COOR ₆	alkyl	alkyl	aryl
H	(CH ₂) _n COOR ₆	alkyl	alkyl	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	alkyl	alkyl	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	alkyl	aryl	H
H	(CH ₂) _n COOR ₆	alkyl	aryl	alkyl
H	(CH ₂) _n COOR ₆	alkyl	aryl	aryl
H	(CH ₂) _n COOR ₆	alkyl	aryl	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	alkyl	aryl	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	H
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	alkyl
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	aryl
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆

H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	H
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	alkyl
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	aryl
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	aryl	H	H
H	(CH ₂) _n COOR ₆	aryl	H	alkyl
H	(CH ₂) _n COOR ₆	aryl	H	aryl
H	(CH ₂) _n COOR ₆	aryl	H	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	aryl	H	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	aryl	alkyl	H
H	(CH ₂) _n COOR ₆	aryl	alkyl	alkyl
H	(CH ₂) _n COOR ₆	aryl	alkyl	aryl
H	(CH ₂) _n COOR ₆	aryl	alkyl	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	aryl	alkyl	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	aryl	aryl	H
H	(CH ₂) _n COOR ₆	aryl	aryl	alkyl
H	(CH ₂) _n COOR ₆	aryl	aryl	aryl
H	(CH ₂) _n COOR ₆	aryl	aryl	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	aryl	aryl	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	H
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	alkyl
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	aryl
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	H
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	alkyl
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	aryl
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
H	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	H	H	H	H
alkyl	H	H	H	alkyl
alkyl	H	H	H	aryl
alkyl	H	H	H	(CH ₂) _n COOR ₆
alkyl	H	H	H	(CH ₂) _n OR ₆
alkyl	H	H	alkyl	H
alkyl	H	H	alkyl	alkyl
alkyl	H	H	alkyl	aryl
alkyl	H	H	alkyl	(CH ₂) _n COOR ₆
alkyl	H	H	alkyl	(CH ₂) _n OR ₆
alkyl	H	H	aryl	H
alkyl	H	H	aryl	alkyl

alkyl	H	H	aryl	aryl
alkyl	H	H	aryl	(CH ₂) _n COOR ₆
alkyl	H	H	aryl	(CH ₂) _n OR ₆
alkyl	H	H	(CH ₂) _n COOR ₆	H
alkyl	H	H	(CH ₂) _n COOR ₆	alkyl
alkyl	H	H	(CH ₂) _n COOR ₆	aryl
alkyl	H	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	H	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	H	H	(CH ₂) _n OR ₆	H
alkyl	H	H	(CH ₂) _n OR ₆	alkyl
alkyl	H	H	(CH ₂) _n OR ₆	aryl
alkyl	H	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	H	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	H	alkyl	H	H
alkyl	H	alkyl	H	alkyl
alkyl	H	alkyl	H	aryl
alkyl	H	alkyl	H	(CH ₂) _n COOR ₆
alkyl	H	alkyl	H	(CH ₂) _n OR ₆
alkyl	H	alkyl	alkyl	H
alkyl	H	alkyl	alkyl	alkyl
alkyl	H	alkyl	alkyl	aryl
alkyl	H	alkyl	alkyl	(CH ₂) _n COOR ₆
alkyl	H	alkyl	alkyl	(CH ₂) _n OR ₆
alkyl	H	alkyl	aryl	H
alkyl	H	alkyl	aryl	alkyl
alkyl	H	alkyl	aryl	aryl
alkyl	H	alkyl	aryl	(CH ₂) _n COOR ₆
alkyl	H	alkyl	aryl	(CH ₂) _n OR ₆
alkyl	H	alkyl	(CH ₂) _n COOR ₆	H
alkyl	H	alkyl	(CH ₂) _n COOR ₆	alkyl
alkyl	H	alkyl	(CH ₂) _n COOR ₆	aryl
alkyl	H	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	H	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	H	alkyl	(CH ₂) _n OR ₆	H
alkyl	H	alkyl	(CH ₂) _n OR ₆	alkyl
alkyl	H	alkyl	(CH ₂) _n OR ₆	aryl
alkyl	H	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	H	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	H	aryl	H	H
alkyl	H	aryl	H	alkyl
alkyl	H	aryl	H	aryl
alkyl	H	aryl	H	(CH ₂) _n COOR ₆
alkyl	H	aryl	H	(CH ₂) _n OR ₆

alkyl	H	aryl	alkyl	H
alkyl	H	aryl	alkyl	alkyl
alkyl	H	aryl	alkyl	aryl
alkyl	H	aryl	alkyl	(CH ₂) _n COOR ₆
alkyl	H	aryl	alkyl	(CH ₂) _n OR ₆
alkyl	H	aryl	aryl	H
alkyl	H	aryl	aryl	alkyl
alkyl	H	aryl	aryl	aryl
alkyl	H	aryl	aryl	(CH ₂) _n COOR ₆
alkyl	H	aryl	aryl	(CH ₂) _n OR ₆
alkyl	H	aryl	(CH ₂) _n COOR ₆	H
alkyl	H	aryl	(CH ₂) _n COOR ₆	alkyl
alkyl	H	aryl	(CH ₂) _n COOR ₆	aryl
alkyl	H	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	H	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	H	aryl	(CH ₂) _n OR ₆	H
alkyl	H	aryl	(CH ₂) _n OR ₆	alkyl
alkyl	H	aryl	(CH ₂) _n OR ₆	aryl
alkyl	H	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	H	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	COOH	H	H	H
alkyl	COOH	H	H	alkyl
alkyl	COOH	H	H	aryl
alkyl	COOH	H	H	(CH ₂) _n COOR ₆
alkyl	COOH	H	H	(CH ₂) _n OR ₆
alkyl	COOH	H	alkyl	H
alkyl	COOH	H	alkyl	alkyl
alkyl	COOH	H	alkyl	aryl
alkyl	COOH	H	alkyl	(CH ₂) _n COOR ₆
alkyl	COOH	H	alkyl	(CH ₂) _n OR ₆
alkyl	COOH	H	aryl	H
alkyl	COOH	H	aryl	alkyl
alkyl	COOH	H	aryl	aryl
alkyl	COOH	H	aryl	(CH ₂) _n COOR ₆
alkyl	COOH	H	aryl	(CH ₂) _n OR ₆
alkyl	COOH	H	(CH ₂) _n COOR ₆	H
alkyl	COOH	H	(CH ₂) _n COOR ₆	alkyl
alkyl	COOH	H	(CH ₂) _n COOR ₆	aryl
alkyl	COOH	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	COOH	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	COOH	H	(CH ₂) _n OR ₆	H
alkyl	COOH	H	(CH ₂) _n OR ₆	alkyl
alkyl	COOH	H	(CH ₂) _n OR ₆	aryl

alkyl	COOH	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	COOH	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	COOH	alkyl	H	H
alkyl	COOH	alkyl	H	alkyl
alkyl	COOH	alkyl	H	aryl
alkyl	COOH	alkyl	H	(CH ₂) _n COOR ₆
alkyl	COOH	alkyl	H	(CH ₂) _n OR ₆
alkyl	COOH	alkyl	alkyl	H
alkyl	COOH	alkyl	alkyl	alkyl
alkyl	COOH	alkyl	alkyl	aryl
alkyl	COOH	alkyl	alkyl	(CH ₂) _n COOR ₆
alkyl	COOH	alkyl	alkyl	(CH ₂) _n OR ₆
alkyl	COOH	alkyl	aryl	H
alkyl	COOH	alkyl	aryl	alkyl
alkyl	COOH	alkyl	aryl	aryl
alkyl	COOH	alkyl	aryl	(CH ₂) _n COOR ₆
alkyl	COOH	alkyl	aryl	(CH ₂) _n OR ₆
alkyl	COOH	alkyl	(CH ₂) _n COOR ₆	H
alkyl	COOH	alkyl	(CH ₂) _n COOR ₆	alkyl
alkyl	COOH	alkyl	(CH ₂) _n COOR ₆	aryl
alkyl	COOH	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	COOH	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	COOH	alkyl	(CH ₂) _n OR ₆	H
alkyl	COOH	alkyl	(CH ₂) _n OR ₆	alkyl
alkyl	COOH	alkyl	(CH ₂) _n OR ₆	aryl
alkyl	COOH	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	COOH	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	COOH	aryl	H	H
alkyl	COOH	aryl	H	alkyl
alkyl	COOH	aryl	H	aryl
alkyl	COOH	aryl	H	(CH ₂) _n COOR ₆
alkyl	COOH	aryl	H	(CH ₂) _n OR ₆
alkyl	COOH	aryl	alkyl	H
alkyl	COOH	aryl	alkyl	alkyl
alkyl	COOH	aryl	alkyl	aryl
alkyl	COOH	aryl	alkyl	(CH ₂) _n COOR ₆
alkyl	COOH	aryl	alkyl	(CH ₂) _n OR ₆
alkyl	COOH	aryl	aryl	H
alkyl	COOH	aryl	aryl	alkyl
alkyl	COOH	aryl	aryl	aryl
alkyl	COOH	aryl	aryl	(CH ₂) _n COOR ₆
alkyl	COOH	aryl	aryl	(CH ₂) _n OR ₆
alkyl	COOH	aryl	(CH ₂) _n COOR ₆	H

alkyl	COOH	aryl	(CH ₂) _n COOR ₆	alkyl
alkyl	COOH	aryl	(CH ₂) _n COOR ₆	aryl
alkyl	COOH	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	COOH	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	COOH	aryl	(CH ₂) _n OR ₆	H
alkyl	COOH	aryl	(CH ₂) _n OR ₆	alkyl
alkyl	COOH	aryl	(CH ₂) _n OR ₆	aryl
alkyl	COOH	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	COOH	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	NHR ₆	H	H	H
alkyl	NHR ₆	H	H	alkyl
alkyl	NHR ₆	H	H	aryl
alkyl	NHR ₆	H	H	(CH ₂) _n COOR ₆
alkyl	NHR ₆	H	H	(CH ₂) _n OR ₆
alkyl	NHR ₆	H	alkyl	H
alkyl	NHR ₆	H	alkyl	alkyl
alkyl	NHR ₆	H	alkyl	aryl
alkyl	NHR ₆	H	alkyl	(CH ₂) _n COOR ₆
alkyl	NHR ₆	H	alkyl	(CH ₂) _n OR ₆
alkyl	NHR ₆	H	aryl	H
alkyl	NHR ₆	H	aryl	alkyl
alkyl	NHR ₆	H	aryl	aryl
alkyl	NHR ₆	H	aryl	(CH ₂) _n COOR ₆
alkyl	NHR ₆	H	aryl	(CH ₂) _n OR ₆
alkyl	NHR ₆	H	(CH ₂) _n COOR ₆	H
alkyl	NHR ₆	H	(CH ₂) _n COOR ₆	alkyl
alkyl	NHR ₆	H	(CH ₂) _n COOR ₆	aryl
alkyl	NHR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	NHR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	NHR ₆	H	(CH ₂) _n OR ₆	H
alkyl	NHR ₆	H	(CH ₂) _n OR ₆	alkyl
alkyl	NHR ₆	H	(CH ₂) _n OR ₆	aryl
alkyl	NHR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	NHR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	NHR ₆	alkyl	H	H
alkyl	NHR ₆	alkyl	H	alkyl
alkyl	NHR ₆	alkyl	H	aryl
alkyl	NHR ₆	alkyl	H	(CH ₂) _n COOR ₆
alkyl	NHR ₆	alkyl	H	(CH ₂) _n OR ₆
alkyl	NHR ₆	alkyl	alkyl	H
alkyl	NHR ₆	alkyl	alkyl	alkyl
alkyl	NHR ₆	alkyl	alkyl	aryl
alkyl	NHR ₆	alkyl	alkyl	(CH ₂) _n COOR ₆

alkyl	NHR ₆	alkyl	alkyl	(CH ₂) _n OR ₆
alkyl	NHR ₆	alkyl	aryl	H
alkyl	NHR ₆	alkyl	aryl	alkyl
alkyl	NHR ₆	alkyl	aryl	aryl
alkyl	NHR ₆	alkyl	aryl	(CH ₂) _n COOR ₆
alkyl	NHR ₆	alkyl	aryl	(CH ₂) _n OR ₆
alkyl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	H
alkyl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	alkyl
alkyl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	aryl
alkyl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	NHR ₆	alkyl	(CH ₂) _n OR ₆	H
alkyl	NHR ₆	alkyl	(CH ₂) _n OR ₆	alkyl
alkyl	NHR ₆	alkyl	(CH ₂) _n OR ₆	aryl
alkyl	NHR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	NHR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	NHR ₆	aryl	H	H
alkyl	NHR ₆	aryl	H	alkyl
alkyl	NHR ₆	aryl	H	aryl
alkyl	NHR ₆	aryl	H	(CH ₂) _n COOR ₆
alkyl	NHR ₆	aryl	H	(CH ₂) _n OR ₆
alkyl	NHR ₆	aryl	alkyl	H
alkyl	NHR ₆	aryl	alkyl	alkyl
alkyl	NHR ₆	aryl	alkyl	aryl
alkyl	NHR ₆	aryl	alkyl	(CH ₂) _n COOR ₆
alkyl	NHR ₆	aryl	alkyl	(CH ₂) _n OR ₆
alkyl	NHR ₆	aryl	aryl	H
alkyl	NHR ₆	aryl	aryl	alkyl
alkyl	NHR ₆	aryl	aryl	aryl
alkyl	NHR ₆	aryl	aryl	(CH ₂) _n COOR ₆
alkyl	NHR ₆	aryl	aryl	(CH ₂) _n OR ₆
alkyl	NHR ₆	aryl	(CH ₂) _n COOR ₆	H
alkyl	NHR ₆	aryl	(CH ₂) _n COOR ₆	alkyl
alkyl	NHR ₆	aryl	(CH ₂) _n COOR ₆	aryl
alkyl	NHR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	NHR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	NHR ₆	aryl	(CH ₂) _n OR ₆	H
alkyl	NHR ₆	aryl	(CH ₂) _n OR ₆	alkyl
alkyl	NHR ₆	aryl	(CH ₂) _n OR ₆	aryl
alkyl	NHR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	NHR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	H	H	H
alkyl	(CH ₂) _n COOR ₆	H	H	alkyl

alkyl	(CH ₂) _n COOR ₆	H	H	aryl
alkyl	(CH ₂) _n COOR ₆	H	H	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	H	H	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	H	alkyl	H
alkyl	(CH ₂) _n COOR ₆	H	alkyl	alkyl
alkyl	(CH ₂) _n COOR ₆	H	alkyl	aryl
alkyl	(CH ₂) _n COOR ₆	H	alkyl	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	H	alkyl	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	H	aryl	H
alkyl	(CH ₂) _n COOR ₆	H	aryl	alkyl
alkyl	(CH ₂) _n COOR ₆	H	aryl	aryl
alkyl	(CH ₂) _n COOR ₆	H	aryl	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	H	aryl	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	H
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	alkyl
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	aryl
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	H
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	alkyl
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	aryl
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	H	H
alkyl	(CH ₂) _n COOR ₆	alkyl	H	alkyl
alkyl	(CH ₂) _n COOR ₆	alkyl	H	aryl
alkyl	(CH ₂) _n COOR ₆	alkyl	H	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	H	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	alkyl	H
alkyl	(CH ₂) _n COOR ₆	alkyl	alkyl	alkyl
alkyl	(CH ₂) _n COOR ₆	alkyl	alkyl	aryl
alkyl	(CH ₂) _n COOR ₆	alkyl	alkyl	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	alkyl	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	aryl	H
alkyl	(CH ₂) _n COOR ₆	alkyl	aryl	alkyl
alkyl	(CH ₂) _n COOR ₆	alkyl	aryl	aryl
alkyl	(CH ₂) _n COOR ₆	alkyl	aryl	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	aryl	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	H
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	alkyl
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	aryl
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆

alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	H
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	alkyl
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	aryl
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COR ₆	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	H	H
alkyl	(CH ₂) _n COOR ₆	aryl	H	alkyl
alkyl	(CH ₂) _n COOR ₆	aryl	H	aryl
alkyl	(CH ₂) _n COOR ₆	aryl	H	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	H	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	alkyl	H
alkyl	(CH ₂) _n COOR ₆	aryl	alkyl	alkyl
alkyl	(CH ₂) _n COOR ₆	aryl	alkyl	aryl
alkyl	(CH ₂) _n COOR ₆	aryl	alkyl	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	alkyl	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	aryl	H
alkyl	(CH ₂) _n COOR ₆	aryl	aryl	alkyl
alkyl	(CH ₂) _n COOR ₆	aryl	aryl	aryl
alkyl	(CH ₂) _n COOR ₆	aryl	aryl	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	aryl	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	H
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	alkyl
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	aryl
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	H
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	alkyl
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	aryl
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
alkyl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	H	H	H	H
aryl	H	H	H	alkyl
aryl	H	H	H	aryl
aryl	H	H	H	(CH ₂) _n COOR ₆
aryl	H	H	H	(CH ₂) _n OR ₆
aryl	H	H	alkyl	H
aryl	H	H	alkyl	alkyl
aryl	H	H	alkyl	aryl
aryl	H	H	alkyl	(CH ₂) _n COOR ₆
aryl	H	H	alkyl	(CH ₂) _n OR ₆
aryl	H	H	aryl	H
aryl	H	H	aryl	alkyl
aryl	H	H	aryl	aryl

aryl	H	H	aryl	(CH ₂) _n COOR ₆
aryl	H	H	aryl	(CH ₂) _n OR ₆
aryl	H	H	(CH ₂) _n COOR ₆	H
aryl	H	H	(CH ₂) _n COOR ₆	alkyl
aryl	H	H	(CH ₂) _n COOR ₆	aryl
aryl	H	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	H	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	H	H	(CH ₂) _n OR ₆	H
aryl	H	H	(CH ₂) _n OR ₆	alkyl
aryl	H	H	(CH ₂) _n OR ₆	aryl
aryl	H	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	H	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	H	alkyl	H	H
aryl	H	alkyl	H	alkyl
aryl	H	alkyl	H	aryl
aryl	H	alkyl	H	(CH ₂) _n COOR ₆
aryl	H	alkyl	H	(CH ₂) _n OR ₆
aryl	H	alkyl	alkyl	H
aryl	H	alkyl	alkyl	alkyl
aryl	H	alkyl	alkyl	aryl
aryl	H	alkyl	alkyl	(CH ₂) _n COOR ₆
aryl	H	alkyl	alkyl	(CH ₂) _n OR ₆
aryl	H	alkyl	aryl	H
aryl	H	alkyl	aryl	alkyl
aryl	H	alkyl	aryl	aryl
aryl	H	alkyl	aryl	(CH ₂) _n COOR ₆
aryl	H	alkyl	aryl	(CH ₂) _n OR ₆
aryl	H	alkyl	(CH ₂) _n COOR ₆	H
aryl	H	alkyl	(CH ₂) _n COOR ₆	alkyl
aryl	H	alkyl	(CH ₂) _n COOR ₆	aryl
aryl	H	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	H	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	H	alkyl	(CH ₂) _n OR ₆	H
aryl	H	alkyl	(CH ₂) _n OR ₆	alkyl
aryl	H	alkyl	(CH ₂) _n OR ₆	aryl
aryl	H	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	H	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	H	aryl	H	H
aryl	H	aryl	H	alkyl
aryl	H	aryl	H	aryl
aryl	H	aryl	H	(CH ₂) _n COOR ₆
aryl	H	aryl	H	(CH ₂) _n OR ₆
aryl	H	aryl	alkyl	H

aryl	H	aryl	alkyl	alkyl
aryl	H	aryl	alkyl	aryl
aryl	H	aryl	alkyl	(CH ₂) _n COOR ₆
aryl	H	aryl	alkyl	(CH ₂) _n OR ₆
aryl	H	aryl	aryl	H
aryl	H	aryl	aryl	alkyl
aryl	H	aryl	aryl	aryl
aryl	H	aryl	aryl	(CH ₂) _n COOR ₆
aryl	H	aryl	aryl	(CH ₂) _n OR ₆
aryl	H	aryl	(CH ₂) _n COOR ₆	H
aryl	H	aryl	(CH ₂) _n COOR ₆	alkyl
aryl	H	aryl	(CH ₂) _n COOR ₆	aryl
aryl	H	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	H	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	H	aryl	(CH ₂) _n OR ₆	H
aryl	H	aryl	(CH ₂) _n OR ₆	alkyl
aryl	H	aryl	(CH ₂) _n OR ₆	aryl
aryl	H	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	H	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	COOH	H	H	H
aryl	COOH	H	H	alkyl
aryl	COOH	H	H	aryl
aryl	COOH	H	H	(CH ₂) _n COOR ₆
aryl	COOH	H	H	(CH ₂) _n OR ₆
aryl	COOH	H	alkyl	H
aryl	COOH	H	alkyl	alkyl
aryl	COOH	H	alkyl	aryl
aryl	COOH	H	alkyl	(CH ₂) _n COOR ₆
aryl	COOH	H	alkyl	(CH ₂) _n OR ₆
aryl	COOH	H	aryl	H
aryl	COOH	H	aryl	alkyl
aryl	COOH	H	aryl	aryl
aryl	COOH	H	aryl	(CH ₂) _n COOR ₆
aryl	COOH	H	aryl	(CH ₂) _n OR ₆
aryl	COOH	H	(CH ₂) _n COOR ₆	H
aryl	COOH	H	(CH ₂) _n COOR ₆	alkyl
aryl	COOH	H	(CH ₂) _n COOR ₆	aryl
aryl	COOH	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	COOH	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	COOH	H	(CH ₂) _n OR ₆	H
aryl	COOH	H	(CH ₂) _n OR ₆	alkyl
aryl	COOH	H	(CH ₂) _n OR ₆	aryl
aryl	COOH	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆

aryl	COOH	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	COOH	alkyl	H	H
aryl	COOH	alkyl	H	alkyl
aryl	COOH	alkyl	H	aryl
aryl	COOH	alkyl	H	(CH ₂) _n COOR ₆
aryl	COOH	alkyl	H	(CH ₂) _n OR ₆
aryl	COOH	alkyl	alkyl	H
aryl	COOH	alkyl	alkyl	alkyl
aryl	COOH	alkyl	alkyl	aryl
aryl	COOH	alkyl	alkyl	(CH ₂) _n COOR ₆
aryl	COOH	alkyl	alkyl	(CH ₂) _n OR ₆
aryl	COOH	alkyl	aryl	H
aryl	COOH	alkyl	aryl	alkyl
aryl	COOH	alkyl	aryl	aryl
aryl	COOH	alkyl	aryl	(CH ₂) _n COOR ₆
aryl	COOH	alkyl	aryl	(CH ₂) _n OR ₆
aryl	COOH	alkyl	(CH ₂) _n COOR ₆	H
aryl	COOH	alkyl	(CH ₂) _n COOR ₆	alkyl
aryl	COOH	alkyl	(CH ₂) _n COOR ₆	aryl
aryl	COOH	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	COOH	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	COOH	alkyl	(CH ₂) _n OR ₆	H
aryl	COOH	alkyl	(CH ₂) _n OR ₆	alkyl
aryl	COOH	alkyl	(CH ₂) _n OR ₆	aryl
aryl	COOH	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	COOH	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	COOH	aryl	H	H
aryl	COOH	aryl	H	alkyl
aryl	COOH	aryl	H	aryl
aryl	COOH	aryl	H	(CH ₂) _n COOR ₆
aryl	COOH	aryl	H	(CH ₂) _n OR ₆
aryl	COOH	aryl	alkyl	H
aryl	COOH	aryl	alkyl	alkyl
aryl	COOH	aryl	alkyl	aryl
aryl	COOH	aryl	alkyl	(CH ₂) _n COOR ₆
aryl	COOH	aryl	alkyl	(CH ₂) _n OR ₆
aryl	COOH	aryl	aryl	H
aryl	COOH	aryl	aryl	alkyl
aryl	COOH	aryl	aryl	aryl
aryl	COOH	aryl	aryl	(CH ₂) _n COOR ₆
aryl	COOH	aryl	aryl	(CH ₂) _n OR ₆
aryl	COOH	aryl	(CH ₂) _n COOR ₆	H
aryl	COOH	aryl	(CH ₂) _n COOR ₆	alkyl

aryl	COOH	aryl	(CH ₂) _n COOR ₆	aryl
aryl	COOH	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	COOH	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	COOH	aryl	(CH ₂) _n OR ₆	H
aryl	COOH	aryl	(CH ₂) _n OR ₆	alkyl
aryl	COOH	aryl	(CH ₂) _n OR ₆	aryl
aryl	COOH	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	COOH	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	NHR ₆	H	H	H
aryl	NHR ₆	H	H	alkyl
aryl	NHR ₆	H	H	aryl
aryl	NHR ₆	H	H	(CH ₂) _n COOR ₆
aryl	NHR ₆	H	H	(CH ₂) _n OR ₆
aryl	NHR ₆	H	alkyl	H
aryl	NHR ₆	H	alkyl	alkyl
aryl	NHR ₆	H	alkyl	aryl
aryl	NHR ₆	H	alkyl	(CH ₂) _n COOR ₆
aryl	NHR ₆	H	alkyl	(CH ₂) _n OR ₆
aryl	NHR ₆	H	aryl	H
aryl	NHR ₆	H	aryl	alkyl
aryl	NHR ₆	H	aryl	aryl
aryl	NHR ₆	H	aryl	(CH ₂) _n COOR ₆
aryl	NHR ₆	H	aryl	(CH ₂) _n OR ₆
aryl	NHR ₆	H	(CH ₂) _n COOR ₆	H
aryl	NHR ₆	H	(CH ₂) _n COOR ₆	alkyl
aryl	NHR ₆	H	(CH ₂) _n COOR ₆	aryl
aryl	NHR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	NHR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	NHR ₆	H	(CH ₂) _n OR ₆	H
aryl	NHR ₆	H	(CH ₂) _n OR ₆	alkyl
aryl	NHR ₆	H	(CH ₂) _n OR ₆	aryl
aryl	NHR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	NHR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	NHR ₆	alkyl	H	H
aryl	NHR ₆	alkyl	H	alkyl
aryl	NHR ₆	alkyl	H	aryl
aryl	NHR ₆	alkyl	H	(CH ₂) _n COOR ₆
aryl	NHR ₆	alkyl	H	(CH ₂) _n OR ₆
aryl	NHR ₆	alkyl	alkyl	H
aryl	NHR ₆	alkyl	alkyl	alkyl
aryl	NHR ₆	alkyl	alkyl	aryl
aryl	NHR ₆	alkyl	alkyl	(CH ₂) _n COOR ₆
aryl	NHR ₆	alkyl	alkyl	(CH ₂) _n OR ₆

aryl	NHR ₆	alkyl	aryl	H
aryl	NHR ₆	alkyl	aryl	alkyl
aryl	NHR ₆	alkyl	aryl	aryl
aryl	NHR ₆	alkyl	aryl	(CH ₂) _n COOR ₆
aryl	NHR ₆	alkyl	aryl	(CH ₂) _n OR ₆
aryl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	H
aryl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	alkyl
aryl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	aryl
aryl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	NHR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	NHR ₆	alkyl	(CH ₂) _n OR ₆	H
aryl	NHR ₆	alkyl	(CH ₂) _n OR ₆	alkyl
aryl	NHR ₆	alkyl	(CH ₂) _n OR ₆	aryl
aryl	NHR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	NHR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	NHR ₆	aryl	H	H
aryl	NHR ₆	aryl	H	alkyl
aryl	NHR ₆	aryl	H	aryl
aryl	NHR ₆	aryl	H	(CH ₂) _n COOR ₆
aryl	NHR ₆	aryl	H	(CH ₂) _n OR ₆
aryl	NHR ₆	aryl	alkyl	H
aryl	NHR ₆	aryl	alkyl	alkyl
aryl	NHR ₆	aryl	alkyl	aryl
aryl	NHR ₆	aryl	alkyl	(CH ₂) _n COOR ₆
aryl	NHR ₆	aryl	alkyl	(CH ₂) _n OR ₆
aryl	NHR ₆	aryl	aryl	H
aryl	NHR ₆	aryl	aryl	alkyl
aryl	NHR ₆	aryl	aryl	aryl
aryl	NHR ₆	aryl	aryl	(CH ₂) _n COOR ₆
aryl	NHR ₆	aryl	aryl	(CH ₂) _n OR ₆
aryl	NHR ₆	aryl	(CH ₂) _n COOR ₆	H
aryl	NHR ₆	aryl	(CH ₂) _n COOR ₆	alkyl
aryl	NHR ₆	aryl	(CH ₂) _n COOR ₆	aryl
aryl	NHR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	NHR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	NHR ₆	aryl	(CH ₂) _n OR ₆	H
aryl	NHR ₆	aryl	(CH ₂) _n OR ₆	alkyl
aryl	NHR ₆	aryl	(CH ₂) _n OR ₆	aryl
aryl	NHR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	NHR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	H	H	H
aryl	(CH ₂) _n COOR ₆	H	H	alkyl
aryl	(CH ₂) _n COOR ₆	H	H	aryl

aryl	(CH ₂) _n COOR ₆	H	H	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	H	H	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	H	alkyl	H
aryl	(CH ₂) _n COOR ₆	H	alkyl	alkyl
aryl	(CH ₂) _n COOR ₆	H	alkyl	aryl
aryl	(CH ₂) _n COOR ₆	H	alkyl	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	H	alkyl	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	H	aryl	H
aryl	(CH ₂) _n COOR ₆	H	aryl	alkyl
aryl	(CH ₂) _n COOR ₆	H	aryl	aryl
aryl	(CH ₂) _n COOR ₆	H	aryl	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	H	aryl	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	H
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	alkyl
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	aryl
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	H
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	alkyl
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	aryl
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	H	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	H	H
aryl	(CH ₂) _n COOR ₆	alkyl	H	alkyl
aryl	(CH ₂) _n COOR ₆	alkyl	H	aryl
aryl	(CH ₂) _n COOR ₆	alkyl	H	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	H	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	alkyl	H
aryl	(CH ₂) _n COOR ₆	alkyl	alkyl	alkyl
aryl	(CH ₂) _n COOR ₆	alkyl	alkyl	aryl
aryl	(CH ₂) _n COOR ₆	alkyl	alkyl	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	alkyl	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	aryl	H
aryl	(CH ₂) _n COOR ₆	alkyl	aryl	alkyl
aryl	(CH ₂) _n COOR ₆	alkyl	aryl	aryl
aryl	(CH ₂) _n COOR ₆	alkyl	aryl	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	aryl	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	H
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	alkyl
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	aryl
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	H

aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	alkyl
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	aryl
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	alkyl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	aryl	H	H
aryl	(CH ₂) _n COOR ₆	aryl	H	alkyl
aryl	(CH ₂) _n COOR ₆	aryl	H	aryl
aryl	(CH ₂) _n COOR ₆	aryl	H	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	aryl	H	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	aryl	alkyl	H
aryl	(CH ₂) _n COOR ₆	aryl	alkyl	alkyl
aryl	(CH ₂) _n COOR ₆	aryl	alkyl	aryl
aryl	(CH ₂) _n COOR ₆	aryl	alkyl	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	aryl	alkyl	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	aryl	aryl	H
aryl	(CH ₂) _n COOR ₆	aryl	aryl	alkyl
aryl	(CH ₂) _n COOR ₆	aryl	aryl	aryl
aryl	(CH ₂) _n COOR ₆	aryl	aryl	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	aryl	aryl	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	H
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	alkyl
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	aryl
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n COOR ₆	(CH ₂) _n OR ₆
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	H
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	alkyl
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	aryl
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n COOR ₆
aryl	(CH ₂) _n COOR ₆	aryl	(CH ₂) _n OR ₆	(CH ₂) _n OR ₆

The invention also relates to a method for the preparation of radiolabeled biomolecules comprising:

5 a) contacting a chelating agent of the invention with a carbonyl moiety of the formula $[M(CO)_3]^+$, wherein M is rhenium (Re) or technetium (Tc), under conditions for forming a chelator-carbonyl complex; and

10 b) contacting the complex with a biomolecule for obtaining a radiolabeled biomolecule. This method is in particular useful for labeling biomolecules that are sensitive to temperature and extreme pH.

This method can for example be performed with a kit, comprising a first vial with the chelating agent of the invention, optionally a first reaction vial for contacting the chelating agent with the carbonyl moiety, a second vial 5 with the biomolecule and optionally a second reaction vial for reacting the biomolecule with the chelator-carbonyl complex obtained in the first step of the reaction.

In an alternative embodiment the invention provides a method for the preparation of radiolabeled biomolecules 10 comprising:

- a) contacting a chelating agent of the invention with a biomolecule for obtaining a chelator-biomolecule.; and
- b) contacting the chelator-biomolecule with a carbonyl moiety of the formula $[M(CO)_3]^+$, wherein M is 15 rhenium (Re) or technetium (Tc) under conditions for forming a radiolabeled biomolecule.

A kit for performing this method comprises for example a first vial with the chelating agent of the invention, optionally a first reaction vial for reacting the 20 chelating agent with the biomolecule, a second vial with the carbonyl moiety and optionally a second reaction vial for reacting the chelator-biomolecule obtained in the first step of the reaction with the carbonyl.

The invention will be further illustrated in the 25 example that follows.

EXAMPLE

Introduction

The bifunctional pyrazolyl-polyamines, pyrazolyl- 30 polythioether, pyrazolyl amino-thioether ligands, pyrazolyl-aminophosphines and pyrazolyl-thioetherphosphines contain different donor atom sets to stabilize the metal and have

different functional groups in different positions to which seeking molecules such as, for example, monoclonal antibodies, peptides, oligonucleotides and glycoproteins, can be coupled. They can also have different substituents and alkyl chains in different positions of the backbone for tuning the physico-chemical properties of the molecules.

A general overview is given in Figure 1, showing possible combinations for metal fragments of the type $[M(CO)_3]^+$ ($M = Re, Tc, Mn$). The five different types of bifunctional tridentate pyrazolyl-containing ligands, which are subject of this invention are depicted schematically in Figure 2.

The present invention will be further illustrated in the Figures 3-6, which are solely intended to clarify the invention. This family of ligands led to thermodynamically stable complexes and the versatility of the backbone is an important factor for tuning the physico-chemical properties of the compounds and obviously its pharmacokinetics. In Figure 6, some of the Re and Tc complexes referred as examples are schematically represented.

Materials and methods

1. Synthesis of 2-[2-(pyrazol-1-yl)ethylimino]ethylamine ($pz(CH_2)_2NH(CH_2)_2NH_2$) (1) (see Figure 3)

A solution of 1-(2-bromoethyl)pyrazole [6d] (12 mmol) in tetrahydrofuran was added dropwise to a solution of ethylenediamine (0.24 mol) in water. The mixture was refluxed for 4 hours. The THF was removed under vacuum and the water phase was washed with dichloromethane. After drying under vacuum resulted a yellow oil which was formulated as $pz(CH_2)_2NH(CH_2)_2NH_2$ (1).

Yield: 50%

$^1\text{H-NMR}$ (D_2O): 7.53 (d, H(3)pz, 1H); 7.45 (d, H(5)pz, 1H);
6.23 (t, H(4)pz, 1H); 4.14 (t, CH_2 , 2H); 2.91 (t, CH_2 , 2H);
2.77 (t, CH_2 , 2H); 2.62 (t, CH_2 , 2H).

5 2. Synthesis $\text{pz}(\text{CH}_2)_2\text{N}[(\text{CH}_2)_3\text{COOH}](\text{CH}_2)_2\text{NH}_2$ (4) (see Figure 3)

2.1. BOC-ON protection

A solution of 1 (1.1 g; 7 mmol) in DMF (20 ml) was cooled to 0°C and a solution of BOC-ON (1.7 g; 7 mmol) in DMF (20 ml) was added dropwise. The reaction mixture was stirred
10 for 3 hours at 0°C . The solvent was removed under vacuum and the solid residue was dissolved in water and washed with chloroform 3 times, yielding 2 as an oil. Yield: 68%. $^1\text{H-NMR}$ (D_2O): 7.55 (d, H(3)pz, 1H); 7.47 (d, H(5)pz, 1H); 6.24 (t, H(4)pz, 1H); 4.38 (t, CH_2 , 2H); 3.40 (t, CH_2 , 2H); 3.20 (t,
15 CH_2 , 2H); 2.99 (t, CH_2 , 2H); 1.25 (s, CH_3 , 9H).

2.2. Alkylation with ethyl 4-bromobutyrate, hydrolysis and deprotection

Compound 2 (757 mg; 3 mmol) was dissolved in 10 ml of
20 acetonitrile. Potassium carbonate (829 mg; 6 mmol) and a catalytic amount of potassium iodide were added to the solution, and ethyl 4-bromobutyrate (858 ml, 16 mmol) was added dropwise. After refluxing for 3 days, the supernatant was separated by filtration and vacuum dried leading to 3.
25 This compound (733 mg, 2 mmol) was dissolved in an aqueous solution of NaOH (800 mg, 20 mmol) and reacted for one day at room temperature. The solution was then neutralized with HCl 1N and vacuum dried. The solid residue was dissolved in methanol, the precipitating salts were filtered off, and the
30 solvent was removed under vacuum, yielding a yellow/brown oil formulated as 4. Yield: (50%).

¹H-NMR (D₂O): 7.78 (d, H(3)pz, 1H); 7.64 (d, H(5)pz, 1H); 6.42 (t, H(4)pz, 1H); 4.36 (t, CH₂, 2H); 3.10 (t, CH₂, 2H); 3.02 (t, CH₂, 2H); 2.86 (t, CH₂, 2H); 2.64 (t, CH₂, 2H); 2.15 (t, CH₂, 2H); 1.68 (q, CH₂, 2H).

5

3. **Synthesis (4-carboxylic)pz(CH₂)₂NH(CH₂)₂NH₂ (7) (see Figure 3)**

3.1. Ethyl N-2-hydroxyethyl-4-pyrazolecarboxylate (5)

Compound 5 was prepared using the classical approach for preparing pyrazoles [7]. Ethyl 2-formyl-3-oxopropionate (2.80 g; 20 mmol) was dissolved in 20 ml of ethanol and cooled to 0°C. 2-Hydroxyethylhydrazine (1.44 g; 20 mmol) was dissolved in 100 ml of ethanol and was added dropwise to the solution of ethyl 2-formyl-3-oxopropionate. The reaction mixture was left overnight at room temperature. The solvent was vacuum removed yielding a yellow oil. Yield: 95%

¹H-NMR (CDCl₃): 7.93 (s, H(3)pz, 1H); 7.91 (s, H(5)pz, 1H); 4.30-4.22 (m, CH₂+OCH₂, 5H); 3.99 (t, CH₂, 2H); 1.30 (t, CH₃, 3H).

20

3.2. Ethyl N-(2-p-toluenesulfonylethyl)-4-pyrazolecarboxylate (6)

Ethyl N-2-hydroxyethyl-4-pyrazolecarboxylate (5) (2.76 g, 15 mmol) and p-toluenesulfonylchloride (2.85 g, 15 mmol) were suspended in a solution of acetone (15 ml) and water (15 ml) and cooled to 0°C. A solution of NaOH (0.6 g, 15 mmol) in water (10 ml) was added dropwise for 15 min. The mixture was then allowed to reach the room temperature and was vigorously stirred overnight. The acetone was evaporated and the aqueous solution was extracted 3 times with chloroform, yielding a yellow oil. Yield: 60%

¹H-NMR (CDCl₃): 7.82 (s, H(3)pz, 1H); 7.76 (s, H(5)pz, 1H); 7.61 (d, H(ph), 2H); 7.26 (d, H(ph), 2H); 4.35 (q, OCH₂, 2H); 4.24 (t, CH₂, 2H); 2.15 (s, CH₃, 3H) 1.33 (t, CH₂, 2H).

Compound 7 was prepared as follows. Ethylenediamine 5 (16 ml; 0.24 mol) was dissolved in a solution of NaOH (9.6 g; 0.24 mol) in water (20 ml). A solution of Ethyl N-(2-p-toluenesulfonylethyl)-4-pyrazolecarboxylate (6) (4.06 g; 12 mmol) in THF (10 ml) was added dropwise to the ethylenediamine solution. The reaction mixture was refluxed 10 for 24 hours. After that, the solvent was vacuum removed and the product was purified by column chromatography in silica-gel (eluent:methanol-NH₃/methanol (50:50)), yielding a dark yellow solid. Yield: 50%.

¹H-NMR (D₂O): δ 7.80 (s, H(3)pz, 1H); 7.64 (s, H(5)pz, 1H); 15 4.27 (t, CH₂, 2H); 3.24 (t, CH₂, 2H); 3.11-3.00 (m, 2CH₂, 4H).
IV (KBr) (ν/cm⁻¹): 1690 (C=O).

4. Synthesis of 3,5-Mepz(CH₂)₂N[(CH₂)₃GlyGlyOEt](CH₂)₂NH₂ (13) (Figure 4)

20 4.1. BOC-ON protection (9)

Compound 8 (3.41 g, 18.71 mmol) [4c] was dissolved in THF (25 mL) and cooled to a temperature between -10°C and 0°C. BOC-ON (4.60 g, 18.71 mmol) in THF (20 ml) was added dropwise and the reaction mixture was stirred for 2 h at 0°C, 25 resulting in the complete conversion of 8 as monitored by TLC (R_f = 0.5, 100% MeOH). The reaction mixture was then warmed to room temperature and partitioned between a saturated aqueous Na₂CO₃ solution and dichloromethane. The organic layer was separated, dried over anhydrous MgSO₄, filtered, 30 and concentrated under reduced pressure to afford the product 9 in quantitative yield (by ¹H-NMR), as a highly viscous

colorless oil. This product was used in the next step without further purification.

¹H-NMR (CDCl₃): δ 5.76 (s, pyrazol, 1H), 5.08 (s br., NH, 1H), 4.04 (t, CH₂, 2H), 3.18 (m, CH₂, 2H), 2.99 (t, CH₂, 2H), 2.72 (t, CH₂, 2H), 2.18 (s, CH₃, 3H), 2.20 (s, CH₃, 3H), 1.40 (s, C(CH₃)₃, 9H).

4.2. Synthesis of 3,5-Me₂pz(CH₂)₂N[(CH₂)₃COOH](CH₂)₂NHBOC (11)

To a stirred solution of the crude product 9 (1.02 g) in CH₃CN (15 mL), ethyl 4-bromobutyrate (1.4 g, 7.20 mmol), K₂CO₃ (1.00 g, 7.20 mmol) and a catalytic amount of KI were added. The obtained suspension was allowed to react under vigorous stirring for 11 days, being the reaction monitored by TLC (*R_f* product = 0.4, 10% MeOH/CH₂Cl₂). After elimination of the white solids in suspension by filtration, the solvent was evaporated in vacuum and a pale-yellow viscous oil was obtained. The crude product was chromatographed on an appropriate column of silica gel with 75-100% ethyl acetate/hexane (gradient) to afford 10 as a pale-yellow viscous oil, which solidifies on standing for several days at room temperature. Yield: 0.73 g (51% yield).

A solution of 10 (4.6 g, 11.60 mmol) in THF (190 mL) and aqueous NaOH (8.3 mL of a 14 N NaOH solution, 116.0 mmol) was refluxed for 8 h. The reaction was monitored by TLC (*R_f* product = 0.2, 10% MeOH/CH₂Cl₂). After neutralization with HCl 4N (pH 6-7), the THF/H₂O solution was evaporated to dryness under reduced pressure. The crude product was chromatographed on an appropriate column of silica gel with 10-50% MeOH/CHCl₃ (gradient) to afford 11 as an highly viscous colorless oil, which crystallizes on standing after several days. Yield: 2.82 g (66%).

Compound 10: $^1\text{H-NMR}$ (CDCl_3): δ 5.75 (s, pyrazol, 1H), 4.09 (q, CH_2 , 2H), 3.98 (s br., CH_2 , 2H), 3.08 (s br., CH_2 , 2H), 2.78 (s br., CH_2 , 2H), 2.45–2.51 (m, CH_2 , 4H), 2.23 (s, CH_3 , 3H), 2.18 (m, CH_3 , CH_2 , 5H), 1.63 (s br., CH_2 , 2H), 1.41 (s, $\text{C}(\text{CH}_3)_3$, 9H), 1.23 (t, CH_3 , 3H).

Compound 11: $^1\text{H-NMR}$ (CDCl_3): δ 5.81 (s, pyrazol, 1H), 4.93 (s br., NH, 1H), 4.12 (t br., CH_2 , 2H), 3.04 (q br., CH_2 , 2H), 2.86 (t br., CH_2 , 2H), 2.58–2.64 (m, CH_2 , 4H), 2.42 (t, CH_2 , 2H), 2.24 (s, CH_3 , 3H), 2.19 (s, CH_3 , 3H), 1.79 (m, CH_2 , 2H), 1.40 (s, $\text{C}(\text{CH}_3)_3$, 9H).

Compound 3,5-Me₂pz(CH_2)₂N[(CH_2)₃CONHGlyGlyOEt](CH_2)₂NH₂ (13) was prepared as follows (see Figure 4).

To a solution of 11 (1.51 g, 4.09 mmol) in CH_3CN (48 mL) were added GlyGly ethyl ester hydrochloride (0.57 g, 4.09 mmol), triethylamine (1.24 g, 12.27 mmol), and HBTU (1.55 g, 4.09 mmol). The reaction mixture was stirred 20 h at room temperature under nitrogen. The reaction was monitored by TLC (R_f product = 0.8, 20% MeOH/ CH_2Cl_2). The solvent was evaporated and the crude product obtained was purified by chromatography on an appropriate silica gel column with 3–5% MeOH/ CHCl_3 (gradient) to afford 12 as a viscous colorless oil. Yield: 1.23 g (59%).

A solution of 3,5-Me₂pz(CH_2)₂N[(CH_2)₃CONHGlyGlyOEt](CH_2)₂NHBOC (12) (1.23 g, 2.41 mmol) in CH_2Cl_2 /TFA (25 mL / 4.1 mL) was allowed to react for 2 h. The reaction was monitored by TLC (R_f = 0.4, 20% MeOH/ CH_2Cl_2). The solvent and the TFA were evaporated under reduced pressure and a highly viscous pale-yellow oil was obtained. This oil was dissolved in water, neutralized with NaOH 1N (pH 7–8) and the solvent evaporated to dryness. TLC: R_f = 0.2, 20% MeOH/ CH_2Cl_2 . The compound was further purified by chromatography on an appropriate silica gel column with 20–40% MeOH/ CHCl_3 .

(gradient) to afford 13 as a viscous colorless oil. Yield: 0.97 g (98 %).

Compound 12: $^1\text{H-NMR}$ (CDCl_3): δ 8.66 (s br., NH, 1H), 7.00 (s br., NH, 1H), 5.80 (s, pyrazol, 1H), 4.91 (s br., NH, 1H) 4.15 (q., CH_2 , 2H), 4.04 (s br., CH_2 , 2H), 3.97 (d, CH_2 , 2H), 3.90 (d, CH_2 , 2H), 2.89 (s br., CH_2 , 2H), 2.69 (s br., CH_2 , 2H), 2.51 (s br., CH_2 , 2H), 2.39 (s br., CH_2 , 2H), 2.30 (s br., CH_2 , 2H), 2.20 (s, CH_3 , 3H), 2.18 (s, CH_3 , 3H), 1.74 (s br., CH_2 , 2H), 1.38 (s, $\text{C}(\text{CH}_3)_3$, 9H), 1.23 (t, CH_3 , 3H).

Compound 13: $^1\text{H-NMR}$ (CD_3OD): δ 5.84 (s, pyrazol, 1H), 4.17 (q, CH_2 , 2H), 4.06 (t, CH_2 , 2H), 3.91 (d, CH_2 , 4H), 2.97 (t, CH_2 , 2H), 2.71-2.80 (m, CH_2 , 4H), 2.51 (t, CH_2 , 2H), 2.25 (s, CH_3 , 3H), 2.15 (s, CH_3 , 3H), 2.12 (t, CH_2 , 2H), 1.66 (m, CH_2 , 2H), 1.25 (t, CH_3 , 3H).

15

5. Synthesis of 3,5-Mepz(CH_2) $_2$ S(CH_2) $_2$ S(CH_2)COOEt (16) (Figure 5)

5.1 Synthesis of 3,5-Mepz(CH_2) $_2$ S(CH_2) $_2$ OH (14)

0.70 ml (10 mmol) of $\text{HSCH}_2\text{CH}_2\text{OH}$ were mixed with 0.40 g (10 mmol) of NaOH, in water, and the solution was refluxed for 5 min. To this solution, 2.78 g (10 mmol) of N-(2-p-toluenesulfonylethyl)-3,5-dimethylpyrazole dissolved in tetrahydrofuran (THF) were added dropwise at room temperature, followed by gentle reflux for 3 hr. The mixture was extracted with chloroform from which, after drying under vacuum, were recovered 1.62g of 14 as a yellow oil (8.10 mmol, 81%).

Compound 14: $^1\text{H-NMR}$ (CDCl_3): 5.67 (s, pz-H, 1H); 4.39 (s, OH, 1H); 4.03 (t, CH_2 , 2H); 3.60 (t, CH_2 , 2H); 2.83 (t, CH_2 , 2H); 2.50 (t, CH_2 , 2H); 2.14 (s, CH_3 , 3H); 2.09 (s, CH_3 , 3H).

5.2 Synthesis of 3,5-Mepz(CH₂)₂S(CH₂)₂Br (15)

0.19 ml (2 mmol) of PBr₃ were added to 14 (0.40 g, 2 mmol) dissolved in chloroform, and the resulting solution was refluxed for 24 hours under N₂. The mixture was treated with 20 ml of 10% NaHCO₃ solution. The organic phase was separated and chloroform removed under vacuum, yielding 0.329 g of 15 as a yellow oil (1.25 mmol, 63%).

¹H-NMR (CDCl₃): 5.82 (s, pz-H, 1H); 4.15 (t, CH₂, 2H); 3.36 (t, CH₂, 2H); 3.00 (t, CH₂, 2H); 2.70 (t, CH₂, 2H); 2.26 (s, CH₃, 3H); 2.23 (s, CH₃, 3H).

Under N₂, dry ethanol was added to metallic sodium (0.15 g, 4.56 mmol), and the mixture was stirred at room temperature until complete conversion to sodium ethoxide. To this mixture an ethanolic solution of ethyl 2-mercaptoacetate (0.50 ml, 4.56 mmol) was added dropwise, followed by addition of 1.20 g (4.56 mmol) of 3,5-Mepz(CH₂)₂S(CH₂)₂Br (15) in ethanol. The reaction mixture was stirring overnight at room temperature. After this time, the solvent was removed under vacuum and the resulting oil was dissolved in chloroform. After washing with water, the organic phase was dried under vacuum yielding 1.00 g of 16 as a yellow oil (3.3 mmol, 72.4%).

Compound 16: ¹H-NMR (CDCl₃): 5.82 (s, pz-H, 1H); 4.14 (m, CH₂, CH₂-COO, 4H); 3.25 (s, CH₂, 2H); 2.92 (t, CH₂, 2H); 2.75 (t, CH₂, 2H); 2.57 (t, CH₂, 2H); 2.2 (s, CH₃, 3H); 2.16 (s, CH₃, 3H); 1.25 (t, CH₃, 3H).

6. Re and Tc compounds (see Figure 6)

6.1. Synthesis of [Re(CO)₃(κ³-pz(CH₂)₂NH(CH₂)₂NH₂)]Br (17a)

100 mg (0.130 mmol) of (NEt₄)₂[ReBr₃(CO)₃] were mixed with 20 mg (0.130 mmol) of the compound 1 (pz(CH₂)₂NH(CH₂)₂NH₂) in water, and the solution was refluxed

For 2 hours. The volume was then reduced under vacuum, and the mixture was left at 4°C until a white solid precipitated.

Yield: >90% by $^1\text{H-NMR}$

$^1\text{H-NMR}$ (D_2O): 7.82 (d, H(3)pz, 1H); 7.76 (d, H(5)pz, 1H);
 5 6.54 (s br, NH, 1H); 6.39 (t, H(4)pz, 1H); 4.86 (s, largo, NH₂, 1H); 4.43 (m, CH₂, 1H); 4.16 (m, CH₂, 1H); 3.94 (s, largo, NH₂, 1H); 3.50 (m, CH₂, 1H); 2.87 (m, CH₂, 1H); 2.71 (m, CH₂, 2H); 2.48 (m, CH₂, 1H); 2.08 (m, CH₂, 1H).

10 6.2. Synthesis of $[\text{}^{99\text{m}}\text{Tc}(\text{CO})_3(\kappa^3\text{-pz}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{NH}_2)]^+$ (17b)

100 μl of a solution of compound 1

(pz(CH₂)₂NH(CH₂)₂NH₂) 10^{-4} M was added to 1 ml of a solution of $[\text{}^{99\text{m}}\text{Tc}(\text{OH})_3(\text{CO})_3]^+$ (1-2 mCi) in phosphate buffer. The solution was incubated for 30 min at 100°C and then analyzed by HPLC.

15 The radiochemical purity was >90%.

6.3. Synthesis of $[\text{Re}(\text{CO})_3(\kappa^3\text{-(4-carboxylic acid)pz}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{NH}_2)]\text{Br}$ (18a)

100 mg (0.130 mmol) of $(\text{NEt}_4)_2[\text{ReBr}_3(\text{CO})_3]$ were mixed
 20 with 26 mg (0.130 mmol) of compound 7, in water, and the solution was refluxed for 2 hours. The volume was then reduced under vacuum, and the mixture was left at 4°C until a white solid precipitated.

Yield: >90% by $^1\text{H-NMR}$

25 $^1\text{H-NMR}$ (D_2O): δ 8.22 (s, H(3)pz, 1H); 8.20 (s, H(5)pz, 1H); 6.62 (s, largo, NH, 1H); 4.94 (s, largo, NH₂, 1H); 4.43 (m, CH₂, 1H); 4.25 (m, CH₂, 1H); 4.05 (s, largo, NH₂, 1H); 3.52 (m, CH₂, 1H); 2.92 (m, CH₂, 1H); 2.76 (m, CH₂, 2H); 2.53 (m, CH₂, 1H); 2.14 (m, CH₂, 1H).

30 IV (KBr) (v/cm^{-1}): 2010 (C=O); 1885 (C=O); 1690 (C=O ligando)

6.4. Synthesis of $[\text{Re}(\text{CO})_3(\kappa^3\text{-3,5-Me}_2\text{pz}(\text{CH}_2)_2\text{N}(\text{CH}_2)_2(\text{glygly})\text{NH}_2)]\text{Br}$ (19a)

100 mg (0.130 mmol) of $(\text{NEt}_4)_2[\text{ReBr}_3(\text{CO})_3]$ were mixed with 53 mg (0.130 mmol) of the ligand 13, in water, and the solution was refluxed overnight.

Yield: 100% by $^1\text{H-NMR}$

$^1\text{H-NMR}$ (D_2O): δ 6.04 (s, H(4)pz, 1H); 5.05 (s, br, NH_2 , 1H); 4.36-4.31 (m, CH_2 , 1H); 4.16-4.04 (m, CH_2 , 1H); 3.88 (s, NHCH_2CO , 2H); 3.84 (s, NHCH_2CO , 2H); 3.65 (s, br, NH_2 , 1H); 3.53 (m, CH_2 , 1H); 3.30 (m, CH_2 , 2H); 2.86 (m, CH_2 , 1H); 2.74 (m, CH_2 , 2H); 2.57 (m, CH_2 , 1H); 2.40 (m, CH_2 , 1H); 2.31 (m, CH_2 , 1H); 2.73 (s, CH_3 , 3H); 2.16 (s, CH_3 , 3H); 2.10 (m, CH_2 , 1H); 1.95 (m, CH_2 , 1H).

6.5. Synthesis of $[\text{}^{99\text{m}}\text{Tc}(\text{CO})_3(\kappa^3\text{-3,5-Me}_2\text{pz}(\text{CH}_2)_2\text{N}(\text{CH}_2)_2(\text{glygly})\text{NH}_2)]^+$ (19b)

100 ml of a solution of 13 (10^{-3} M) was added to 1 ml of a solution of $[\text{}^{99\text{m}}\text{Tc}(\text{OH})_3(\text{CO})_3]^+$ (1-2 mCi) in phosphate buffer. The solution was incubated for 1h at 100°C and then analysed by HPLC. The radiochemical purity was $>90\%$.

7. Synthesis of pyrazolyl-aminophosphines (figure 7)

The preparation of the pyrazolyl-aminophosphines of the invention involves alkylation of 1-(2-aminoethyl)pyrazoles with (2-bromoethyl)phosphonic acid diethyl ester, yielding a pyrazole-amino-phosphonate derivative (compound a). Reduction of compound a with lithium aluminium hydride (LAH) affords a primary phosphine (compound b) which is then converted to the final chelator (compound c) by treatment with formaldehyde in acidic medium (Katti et al., J. Am. Chem. Soc. 122, 1554 (2000)).

8. Synthesis of pyrazolyl-thioetherphosphines (figure 8)

The preparation of pyrazolyl-thioetherphosphines of the invention involves reaction of 1-(2-mercaptoethyl)pyrazoles with (2-bromoethyl)phosphonic acid diethyl ester yielding a pyrazole-thioether-phosphonate derivative (compound d) (Katti et al., Angew. Chem. Int. Ed. 38, 2020 (1999). Reduction of compound d with lithium aluminium hydride, followed by treatment of the resulting primary phosphine (compound e) with formaldehyde in acidic medium affords the final chelator (compound f).

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